Universidade de Lisboa

Faculdade de Farmácia

Tuberculose, o que há de novo.

Iuliia Potapova

Mestrado Integrado em Ciências Farmacêuticas

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Monografia de Mestrado Integrado em Ciências Farmacêuticas apresantada á Universidade de Lisboa através da Faculdade da Farmácia

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Ano 2019

Agradecimentos

Agradeço à minha família, amigas, colegas de trabalho que assistiram ao meu percurso e evolução. Agradeço pelo apoio que me deram, pela paciência e pelo carinho.

Agradeço ao meu pai, que foi impulsionador desta escolha de tema, visto ter sido ele também uma das pessoas afectadas pela doença no seu percurso profissional enquanto médico.

Agradeço à minha Professora-orientadora Ana Paula Francisco o constante apoio para a conclusão desta etapa tão importante.

Agradeço a Portugal inteiro que me deu, para mim e para a minha família, a oportunidade de mudar a minha vida para melhor.

CONTENTS

Nas últimas décadas, desde a reemergência da tuberculose (tb) no mundo, o ano de 2015 tornou-se um novo marco na história dessa doença, quando a organização Mundial da saúde (OMS) propôs acabar com a tuberculose como um problema de saúde pública.

O recrudescimento da tuberculose em consequência da epidemia de AIDS e os seus efeitos devastadores nas pessoas vivendo com o HiV – dentre eles a alta letalidade e o aumento de casos de tuberculose resistente aos medicamentos – e a concentração da tuberculose em populações vulneráveis socialmente, levaram à priorização no combate à doença, seja em nível global ou nacional.

Pela primeira vez em décadas, surgem novidades nos campos diagnósticos e terapêuticos: testes rápidos moleculares, novos fármacos desenvolvidos especificamente para o tratamento da tiberculose, inúmeras vacinas preventivas e terapêuticas em fase de desenvolvimento, novos regimes encurtados sendo testados em ensaios clínicos multicêntricos, enfim, em um cenário sempre tão carente de novidades, começa a florescer a esperança

A nova estratégia, além de metas extremamente ousadas, traz o enfrentamento dos determinantes sociais e a inovação como base de seus três pilares. A inovação está presente na atenção centrada nos pacientes, no estímulo crescente à pesquisa e à adoção de novas tecnologias e na introdução de um novo componente capaz de potencializar o efeito das demais medidas: a utilização da proteção social como ferramenta de apoio aos pacientes e às comunidades afetadas. Passa-se, efetivamente, a encarar a tuberculose como um fenômeno multicausal que extrapola o campo biomédico.

SUMÁRIO

A tuberculose é um importante problema de saúde pública,tendo uma prevalência global,e podendo mesmo provocar a morte.Esta situação ganha ainda mais importância com advento da resistência ao antibióticos,bem como à crescente desigualdade social que se tem verificado em países cujo desenvolvimento está mal sustentado,como Leste da Europa e África.A doença também afeta países desenvolvidos com o movimento migratório e cada vez mais trânsito entre cidadãos de várias partes do mundo. A OMS informou que foram notificados casos em seis países: França, Japão, Holanda, Portugal, Coreia do Sul e Eslováquia.

Este trabalho surge no sentido de perceber que novas abordagens terapêuticos existem,seja no que diz respeito a fármacos como aos seus esquemas terapêuticas.

Em conclusão o tratamento que ainda passa pela rifampicina e isoniazida deve ser avaliado de acordo com a susceptibilidade da micobactéria que definará a dose ou eventuais combinações destes ou outros fármacos.
Palvras chaves-Tuberculose,Mycobacterium,Tratamento,HIV,Resistência.

ABSTRACT

Tuberculosis is a major public health problem, with a global prevalence, which may cause even death of infected people. This situation becomes even more important considering antibiotic resistance, as well as the growing social inequality in countries with unstable development, such as Eastern Europe and Africa. The disease also affects developed countries due to increasing human migration and subsequent transit of citizens from various parts of the world. WHO reported tuberculosis cases in six countries: France, Japan, the Netherlands, Portugal, South Korea, and Slovakia.

This work gives the understanding of new therapeutic approaches with regard to the drugs and its therapeutic schemes as well.

In conclusion, the regimens still containing rifampicin and isoniazid should be evaluated according to its effectiveness against Mycobacterium and define the dose or possible combinations of these or other drugs.
Keywords-Tuberculosis, Mycobacterium, Treatment, HIV, Resistance.

INTRODUCTION

Mycobacteria are small rod-shaped bacilli that can cause a variety of diseases in humans. They can be divided into three main groups:

– *Mycobacterium tuberculosis* complex: this group includes *M. tuberculosis, M. bovis, M. africanum, M. microti*, and *M. canetti*. They all can cause "tuberculosis" in humans. The vast majority of tuberculosis is caused by *M. tuberculosis*, with the other organisms being relatively rare. Their treatment is similar (with *M. bovis* being innately resistant to pyrazinamide and *M. africanum* being innately resistant to thioacetazone).

This guide only addresses disease caused by *Mycobacterium tuberculosis* complex.

– *Mycobacterium leprae* causes leprosy.

– Non tuberculous mycobacteria (NTM): this group includes all the other mycobacteria that can cause diseases in humans. NTM sometimes can cause clinical manifestations (in the lungs, skin, bones, or lymph nodes) similar to those of tuberculosis. Most NTM exist in the environment, are not usually spread from person to person and are often non-pathogenic in persons with intact immune system or healthy lung tissue.

All mycobacteria are classical acid-fast organisms and are named so because of the stains used in evaluation of tissue or sputum specimens (i.e. Ziehl-Neelsen stain,).

M. tuberculosis multiplies more slowly than the majority of bacteria; this is why tuberculosis has a slower evolution (causes disease weeks or even months to years after infection) than most other bacterial infections.

M. tuberculosis is a strictly aerobic bacterium. It therefore multiplies better in pulmonary tissue (in particular at the apex, where oxygen concentration is higher) than in the deeper organs.

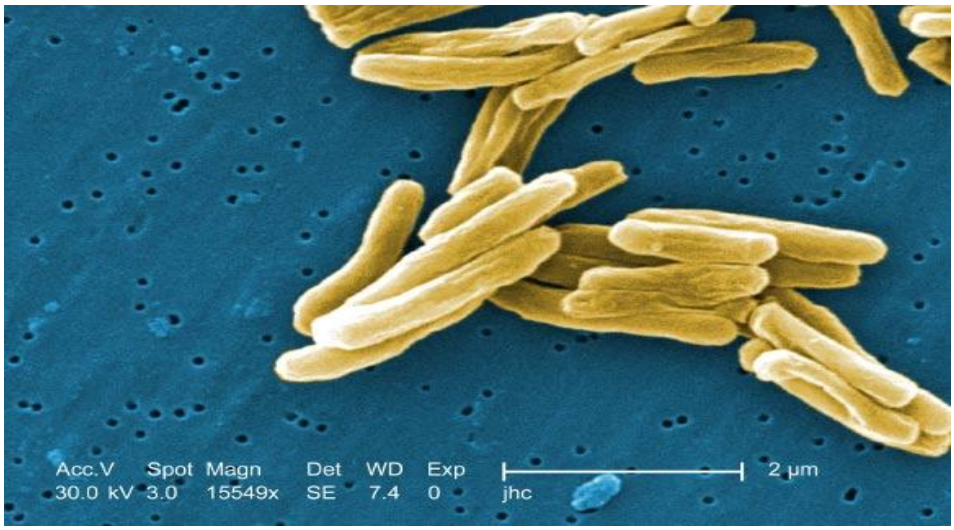

Fig.1. Mycobacterium tuberculosis scanning electron micrograph
http://textbookofbacteriology.net/tuberculosis.html

Transmission

M. tuberculosis is transmitted from human-to-human and is mainly spread by airborne route. The source of infection is a patient with pulmonary or laryngeal tuberculosis (TB) who expectorates bacilli. During coughing, speaking, or sneezing, the patient produces tiny infectious droplets. These particles, called droplet nuclei, are about 1 to 5 microns in diameter—about 1-5/1000 of millimetre. Droplet nuclei can remain suspended in the air for several hours, depending on the environment.

Transmission may occur when these infectious droplets are inhaled. Sunlight, UV light and ventilation are effective in decreasing the ability of the droplets reaching the lung. The other modes of transmission are far less common. Cutaneous or mucous inoculation rarely occurs, although such cases have been observed in laboratory personnel. A rare cause of digestive transmission of TB can occur with *M. bovis*, most commonly through cow's milk.

The infectiousness of a patient is linked to the quantity of bacilli contained in his sputa. Patients with sputum smear-positive microscopy are by far the most contagious. Those with smear-negative/culture-positive results are less contagious. Patients whose sputum smear microscopy and culture are negative are usually not contagious.

Patients who are infected with *M. tuberculosis*, but do not have active disease, cannot transmit TB. Extrapulmonary (EP) forms of TB are only contagious in exceptional circumstances. Children are generally much less contagious than adults. This may be due to weaker cough mechanics, less sputum production and lower bacillary load.

Not everyone who is exposed to an infectious TB patient becomes infected with *M. tuberculosis*. The probability that TB will be transmitted depends on three factors:

Contagiousness of the source (the greatest factor):

– Bacteriological status: smear-positive being the most infectious;

– Virulence of the tubercle bacilli: certain strains are very transmissible (and/or more likely to cause active disease).

Environment where the exposure occurred:

– Open air and sunlight are conditions less likely to lead to transmission, whereas small rooms/settings with no ventilation are the conditions most likely to lead to transmission.

– The proximity of the person to the patient is also important (i.e. sleeping next to the patient in the ward versus sleeping 20 meters away).

Duration of exposure:

Close contacts of TB patients are at highest risk of becoming infected with *M. tuberculosis*. They may be family members, roommates, friends, co-workers or others who spend multiple hours per day with the TB patient while the person is infectious.

The best way to stop transmission is to start giving patients effective TB treatment as soon as possible. The length of time required for a TB patient to become non-infectious after starting TB therapy is not exactly known. However, once an effective TB therapy is started, as long as the patient follows the prescribed treatment regimen, there is considerable evidence showing the infectiousness can rapidly decline, even after a few days

Evolution of TB infection and disease in humans

When a person inhales infectious droplets containing *M. tuberculosis*, most of the larger droplets become lodged in the upper respiratory tract (nose and throat), where infection is unlikely to develop. However, smaller droplet nuclei may reach the small air sacs of the lung (the alveoli), where infection may begin.

Primary infection

After transmission, *M. tuberculosis* multiplies slowly, in most cases in the terminal alveoli of the lungs (primary focus) and in the lymph nodes of corresponding drainage areas: this represents the primary infection. The primary focus and related hilar lymphadenopathy form the primary complex.

In one to two months, due to the action of lymphocytes and macrophages (cellular immunity), the primary focus will be contained and encapsulated with a central zone of parenchymal necrosis (caseous necrosis). It is at this moment that specific TB immunity appears, and a positive skin reaction to tuberculin is observed. This stage is usually asymptomatic; however, in some rare cases, hypersensitivity reactions may occur.

Note: a small area of granulomatous inflammation will occur in the alveoli, which is not usually detectable on chest X-ray unless it calcifies or grows substantially. It is called a primary focus.

In the majority of cases (90 to 95% of non-HIV infected patients), the pulmonary lesions gradually heal. In 5 to 10% of the cases, the pulmonary lesion will progress to active disease either by gradual progression and/or spread via lymphatics or blood or by reactivation (often many years later) of primary or secondary lesions.

Active TB

Before immunity is established, bacilli from the primary infectious focus or from a near-by lymph node can be transported and disseminated throughout the body via the lymph system or the bloodstream. Secondary foci containing bacilli can be born this way, particularly in the lungs, lymph nodes, serous membranes, meninges, bones and kidneys. As soon as an immune response

is mounted, most of these foci spontaneously resolve. Yet, a number of bacilli may remain latent in the secondary foci for months or even years

Different factors can reduce immunity (e.g. HIV infection) and lead to reactivation of the bacilli and their multiplication in one or more of these foci. This reactivation or progression of the primary or secondary foci results in “active TB disease”.

While active TB may occur after months or years without clinical signs following primary infection, it is estimated that half of the cases of active TB appear in the year following infection.

Risk factors for developing active TB

The risk depends on a number of factors including those that lead to a weakened immune system, damaged lungs, or the intensity and duration of exposure:

Host immune defences:

– HIV infection (risk multiplied by 20-40);

– Diabetes mellitus (risk multiplied by 3-5);

– Malnutrition;

– Prolonged therapy with corticosteroids (such as prednisolone) and other immuno - suppressive therapies;

– Certain types of cancer (e.g., leukaemia, Hodgkin's lymphoma, or cancer of the head and neck);

– Severe kidney disease;

– Alcoholism;

– Substance abuse;

– Age:

• Young children (children under 5 have twice the risk and higher risks are observed for those under 6 months);

• Persons over sixty years have 5 times the risk;

– Pregnancy.

Conditions that damage the lung:

– Tobacco smoking;

– Silicosis.

Intensity of exposure (number of inhaled bacilli):

– Contagiousness of the source;

– Environment and proximity in which the exposure took place;

– Duration of exposure;

– Residents and employees of high-risk congregate setting.

Prognosis

TB is a severe and often deadly disease without treatment. After 5 years without treatment, the outcome of smear-positive pulmonary TB (PTB) in HIV-negative patients is as follows:

– 50-60% die (case fatality ratio for untreated TB);

– 20-25% are cured (spontaneous cure);

– 20-25% develop chronic smear-positive TB.

With adequate treatment, the case fatality ratio (CFR) often falls to less than 2 to 3% under optimal conditions.

Similar CFRs are seen with untreated EPTB and smear-negative PTB, with an equivalent fall in CFR with adequate treatment.

Untreated TB in HIV-infected patients (not on antiretrovirals) is almost always fatal. Even on antiretrovirals, the CFR is higher than in non-HIV infected patients

Factors modifying TB epidemiology

There are four major factors that influence TB epidemiology: (1) socioeconomic development; (2) TB treatment; (3) HIV infection; and (4) BCG vaccination.

Socioeconomic development-

In European countries, the incidence and specific mortality of TB have diminished by 5 to 6% per year since 1850. This progressive improvement dates back to before the era of vaccination and antibiotics and was correlated with socioeconomic development (improvement of living conditions, nutritional status of populations, etc.). TB is a disease of the poor: over 95% of cases occur in resource-constrained countries and in poor communities. In industrialised countries, TB generally affects the most disadvantaged social groups.[1]

In general, the basic principles of TB treatment are as follows: treatment with several drugs in adequate doses for a sufficient time. Unfortunately, these principles have been forgotten by doctors, TB control programs, and especially government financial agencies. As a result of this, errors are very common in the treatment of patients with MDRTB, and seeking expert advice is always justified. Clinical guidelines for the diagnosis and treatment of patients with respiratory tuberculosis provide a complete description of anti-TB drugs[2].Chemotherapy allows

in difficult modern epidemiological conditions to achieve clinical cure in patients with tuberculosis of various localization. One of the reasons for ineffective treatment (separation from treatment) is the refusal of patients to continue treatment due to the development of adverse reactions to anti-TB drugs. Patients themselves often have a low level of social claims and an unstable attitude to continue treatment. In this regard, one can speak with a certain degree of confidence about the role of adverse reactions in the formation of multidrug-resistant tuberculosis of mycobacteria. In this context, the problem of adverse reactions in phthisiology is no longer just a medical problem, it becomes a socio-economic problem. Therefore, knowledge of the clinical manifestations of adverse reactions to anti-TB drugs is one of the conditions for rational chemotherapy, prevention of adverse reactions, as well as their elimination.

The incidence of side effects of etiotropic therapy for tuberculosis ranges from 13-17 to 62-65%. Such a wide range is explained by the difference in the studied groups according to their social and epidemiological status, different environmental conditions in different regions of the country, which, undoubtedly, affects the incidence of undesirable effects during anti-TB treatment.

The aim of the study is to analyze the latest techniques and drugs used to treat tuberculosis. More detailed subjects include:

the analysis of existing anti-TB drugs

the characterization of the effectiveness of existing anti-TB drugs

the analysis of the main directions of innovation in the treatment of tuberculosis

the characterization of the evaluation of the effectiveness of innovative practices

the analysis of new drug targets and antimycobacterial agents in discovery .

CHAPTER 1. ACTUAL METHODS OF TREATING TUBERCULOSIS

1.1. Typology of existing anti-TB drugs

Modern chemotherapy has firmly taken a leading place in the treatment of tuberculosis patients.

The classification of anti-TB drugs (International Anti-TB Union) suggests the following division of anti-TB drugs.

I. The most effective drugs- the synthetic drug isoniazid (GINC) and antibiotic rifampicin.

II. Moderately effective drugs

Antibiotics: streptomycin, kanamycin, florimycin (viomycin), fluoroquinolones, cycloserine.

Synthetic preparations: ethambutol, ethionamide, protionamide, pyrazinamide.

III. Less effective drugs

Synthetic preparations: PASK tibone (thioacetasone)

In the 1997 United States Infectious Diseases Textbook, the following drug groups are identified:

- first-line drugs - isoniazid, rifampicin, streptomycin, pyrazinamide and ethambutol;
- second-line drugs - ethionamide, cycloserine, capreomycin and kanamycin;
- alternative drugs - rifabutin, amikacin, ciprofloxacin and ofloxacin.

The problem of multidrug-resistant and extensively drug-resistant tuberculosis (MDR / XDR-TB) has "expanded" the list of drugs used in the treatment of tuberculosis, and in the WHO programmatic guide for drug-resistant tuberculosis (2007), TB drugs were grouped as follows (Table 1.1.).

Table 1.1. Classification of anti-TB drugs

Group 1. First-line anti-TB drugs	Isoniazid (H); rifampicin (R); ethambutol (E); pyrazinamide (Z)
Group 2. Injectable anti-TB drugs	Streptomycin (S); kanamycin (Km); amikacin group anti-TB drugs (Am); capreomycin (Cm); Viomycin (Vi)
Group 3. Fluoroquinolones	Ciprofloxacin (Cfx); ofloxacin (Ofz); levofloxacin (Lfz); moxifloxacin (Mfz) a; gatifloxacin (Gfz)
Group 4. Second-line anti-TB drugs with bacteriostatic effect and intended for oral use	Ethionamide (Eto); protionamide (Pto); cycloserine (Cs); terizidone (Trd); PASK (PAS), thioacetasone (Th) b
Group 5. Anti-TB drugs of unclear activity (not recommended by WHO for routine use in MDR-TB patients)	Clofacimin (Cfz); amoxicillin / clavulanate (Amx / Clv); clarithromycin (Clr); linezolid (Lzd)

In recent years, two new anti-TB drugs have appeared - perchlozone (Tp) and bedaquiline (Bq).

The group of anti-TB drugs includes a number of natural and semi-synthetic compounds. According to the generally accepted classification, anti-TB drugs are divided into drugs of the first row (main) and the second row (reserve)[3].

This systematization is due to differences in their activity and toxicity. Group I drugs combine high activity against M. tuberculosis and moderate toxicity. Second-line drugs are characterized by either less activity, or higher toxicity, or both. First-line drugs are used to treat patients with newly diagnosed tuberculosis, second-line drugs - with inefficiency or poor tolerance of the main drugs.

The properties of the individual drugs included in this classification (rifampicin, aminoglycosides, fluoroquinolones) are described above in the relevant chapters and therefore are not considered in this section.

Some of the anti-TB drugs, due to the characteristics of the activity spectrum, are also used for other infections caused by mycobacteria (leprosy, etc.).

Based on the first-line anti-TB drugs — isoniazid, rifampicin, pyrazinamide, ethambutol — a number of combined tablet preparations have been created, such as rifinag, rifater, rifacomb, mayrin, mayrin P, phthisoetam, phthisopyram . The main goal of the development and use of these drugs is to reduce the daily number of tablets taken by the patient, and to ensure higher compliance on this basis.

It should be emphasized that chemotherapy for tuberculosis differs from the generally accepted methods of using various antibacterial drugs for other acute and chronic infections. Etiotropic treatment has to be carried out systematically and for a long time. This is due to the biological characteristics of mycobacteria, the significant prevalence and severity of specific and non-specific tissue lesions. A significant role is also played by the low rate of reparative processes, especially in chronic forms of the disease. The same reasons determine another condition for the effectiveness of treatment - the need to combine chemotherapy with various pathogenetic agents that contribute to the growth of the body's resistance to infection[4].

Anti-TB drugs are also distributed according to their degree of effectiveness. Isoniazid, which is the main drug, has the highest bacteriostatic activity, especially in the treatment of newly diagnosed patients with tuberculosis, and then rifampicin. The remaining drugs are distributed according to activity as follows: streptomycin> kanamycin> pyrazinamide> ethionamide = protion - amide> ethambutol> cycloserine> florimycin> PASK> thioacetazone.

Most anti-TB drugs act on bacteriostatic mycobacterium tuberculosis, inhibiting their reproduction and reducing their virulence. Isoniazid and rifampicin can act bactericidal in high concentrations.

To obtain a lasting therapeutic effect and prevent possible relapses, anti-TB drugs should be used for a long time. The choice of drugs and the duration of their use depend on the form of tuberculosis and its course, previous treatment, the sensitivity of tuberculosis mycobacteria to the drug, its tolerance, etc. When combining drugs, 1 or 2 drugs of the first row should be kept in

combination, especially isoniazid, if there are no contraindications or drug resistance to it. With combined use, the dose of each of the drugs taken is usually not reduced.

The HIV epidemic has partially led to a resurgence of TB and vice versa. Worldwide, about one third of deaths among people with a positive HIV test are due to TB. The diagnosis of TB can be difficult in patients with AIDS (the outcome of HIV), because often instead of upper lobe cavity infiltrates typical of disease reactivation, they may reveal signs more characteristic of primary TB with intrathoracic lymphadenopathy, lower lobe infiltrates, pleural effusion, or even normal radiographic picture. Typically, these patients have symptoms: cough, fatigue, weight loss, night sweats. But at the same time, the symptomatology in patients with TB and AIDS can be so nonspecific that in many hospitals in the USA any patient with AIDS is isolated if he has changes in the chest radiograph. Such an arrangement certainly ensures more successful TB detection, but it contributes to the overload of many institutions with disabilities, especially if the prevalence of TB is low, and this is practically not applicable in most developed countries.

A practical problem arises if it is not clear to the clinician that the patient has MTB or Mycobacterium avium complex (MAC), or both. MAC usually affects AIDS patients with CD4 counts of less than 50, while TB can occur in a patient with any CD4 counts. Current treatment for MAC differs from that for MTB in that the main drug for MAC is macrolide, usually clarithromycin, and EMB and rifabutin have some activity against both diseases. IND and PZA are useless for MAC, and clarithromycin is not indicated for MTB[5].

In approximately 90% of MAC cases in HIV patients, the lungs remain intact, and the intestines, bone marrow, liver and spleen are affected. In turn, TB in AIDS patients, according to a rough estimate, in one third of cases involves only the lungs, in one third it is purely extrapulmonary, and in one third it is mixed. A typical MAC picture is usually a cachectic AIDS patient with chronic symptoms of exhaustion, fever, abdominal pain, diarrhea, but without any significant changes in the chest radiograph. On examination, these patients are pale, of poor nutrition with an enlarged liver and spleen; severe anemia (Hb of the order of 7) and elevated liver function tests are usually observed.

If you have doubts about MAC or TV, then rifabutin, IND, PZA, EMB and clarithromycin can be used until the clinical picture is clarified or the results of culture are known. In general, if a CUB in an AIDS patient is detected in sputum, then TB should be assumed and appropriate treatment should be prescribed by sampling the cultures.

The clinical picture has changed slightly over the past few years due to the start of the use of protease inhibitors, which appear to globally reduce the retroviral pool of microorganisms in HIV patients, while significantly increasing the CD4 content. This led to the "immune recovery" syndrome, which leads to a change in the clinical picture of mycobacteriological disease. For

example, MTB can give a picture that is more similar to reactivation, rather than to “primary TB”. The effect on the MAC is even more pronounced.

By their effect, protease inhibitors restore the body's defense mechanisms. Thus, it is very important to ask the patient if he is receiving protease inhibitors, since they greatly change the picture of mycobacterial disease. Of course, it is always useful to repeat the CD4 assay and use it as a “calibration tool” in assessing the patient’s immune response.

The clinician should also always be alert for patients with pneumonia caused by Pneumocystis carinii (PCP) with adherent TB and vice versa. With PCP, pleural effusions, asymmetric infiltrates, or intrathoracic lymphadenopathy are rare, all that is typical of TB. In turn, TB is rarely represented by diffuse, bilateral, symmetrical infiltrates, so typical of PCP. Bacterial sepsis is also possible along the course of TB.

Another clinical situation to keep in mind is when an AIDS patient has both lung and brain damage. Of course, this may be due to TB, but it can also be a manifestation of Nocardia, anaerobic and staphylococcal abscess, lymphoma and, less commonly, toxoplasma or fungi. Although most adults with TB have symptoms, patients of extreme ages may not have symptoms at all, they may be mild or very nonspecific.

In about half of the children, the disease is asymptomatic. Young children also do not produce sputum, the disease begins with a small number of mycobacteria, and chest x-rays are difficult to interpret. In addition, HIV is difficult to diagnose in young children, TKT may be unreliable, and the source case is often not found. Thus, managing TB in children requires a large share of clinical decisions and expert opinion.

On the other hand, in older people, symptoms may be few, confused with existing cardiopulmonary symptoms, or be extremely non-specific in their manifestation, such as low fever, decreased appetite, and weight loss. TB can easily be mistaken for cancer, unresolved pneumonia, chronic obstructive pulmonary disease, sepsis, depression and dementia, and can develop simultaneously with these conditions, in particular with cancer.

It is noteworthy that the percentage of TB detected by autopsy has not changed over the past 20 years and remains 5% with the vast majority of such findings in the elderly. According to some reports, mortality from TB is at least 30% in the elderly (over 65) and, therefore, the closest consideration is required regarding the presence of this serious disease in an elderly person with an unclear picture of the disease.

In contrast to pulmonary TB, there are very few full-fledged clinical studies, the results of which could lead the clinician in choosing the treatment for extrapulmonary disease. The usual recommendation is to treat it in the same way as pulmonary, and the most common form of extrapulmonary TB - damage to the pleura alone - is usually abacillary and therefore lends itself

well to short-course therapy. The same can be said of primary tuberculosis without pulmonary infiltrates, but with intra-thoracic lymphadenopathy, as in many children. In addition, simple radiography makes it easy to observe the dynamics of effusion or lymph nodes. But the described approach is not applicable for other forms of extrapulmonary TB, when it is difficult to monitor the dynamics of the process.

Side effects of anti-TB drugs, especially second-line drugs in AIDS patients, require careful study and a large share of clinical decisions. On the one hand, the patient can be persuaded to endure some gastrointestinal discomfort, itching or dizziness, at the same time, on the other hand, a temporary cessation of medication and / or correction of therapy can help to avoid deafness, blindness, liver or kidney failure. In addition, significant drug interactions are upsetting often, especially with RIF, and contribute to soreness and mortality in this patient population.

Surgical treatment can often help with MDRTB, when the main bacterial pool is localized and therefore can be mostly removed by resection, the patient is not burdened with regard to operational risk and experienced surgeons are available.

CHAPTER 2. INNOVATIVE METHODS OF TREATING TUBERCULOSIS

2.1. The main directions of innovation in the treatment of tuberculosis

Over the course of more than a 50-year period of the use of anti-TB drugs a clinical approach has been carried out to assess the effectiveness of chemotherapy, where the main task has always been to achieve not only the cessation of bacterial excretion, but also the complete elimination of the clinical manifestations of the disease and the persistent healing of tuberculous changes in the affected organ, as well as the maximum restoration of impaired body functions.

The therapeutic effect of chemotherapy is due to the antibacterial effect of anti-TB drugs and is aimed at suppressing the multiplication of tuberculosis mycobacteria (bacteriostatic effect) or their destruction (bactericidal effect) in the patient. Only by suppressing the multiplication of mycobacterium tuberculosis or their destruction is possible to launch adaptive mechanisms aimed at activating reparative processes and creating conditions for complete clinical cure.[6].

The clinical effectiveness of anti-TB drugs is determined by many factors, among which the main ones are:

massiveness of the mycobacterial population itself;

the sensitivity or resistance of mycobacteria to the drugs used;

the ability of mycobacteria to reproduce rapidly;

the level of bacteriostatic concentration created;

the degree of penetration of drugs into the affected areas and activity in them;

the ability of drugs to act on extra- and intracellular (phagocytosed) microbes;

drug tolerance[7].

The main anti-TB drugs: isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E) and streptomycin (S) are highly effective against mycobacteria that are sensitive to all anti-TB drugs.

The question of conducting etiotropic treatment in patients with drug-resistant pulmonary tuberculosis is much more difficult, when the frequency and nature of drug resistance of mycobacterium tuberculosis is the most important and determining clinical effect of chemotherapy.

According to the existing WHO classification, mycobacterium tuberculosis can be:

monoresistant to one anti-TB drug;

multiresistant to two or more anti-TB drugs, but not to the combination of isoniazid and rifampicin;

multiple resistant, at least to a combination of isoniazid and rifampicin.

Specific lung lesions in patients with multidrug resistance of tuberculosis mycobacteria are especially difficult.

The main risk factor for the development of drug resistance of mycobacterium tuberculosis is an ineffective previous treatment, especially interrupted and incomplete. In this regard, the main task in preventing the development of drug resistance is the correct treatment of newly diagnosed patients using modern scientifically-based and evidence-based chemotherapy regimens.

In the treatment of drug-resistant pulmonary tuberculosis, reserve anti-TB drugs are used: kanamycin (K), amikacin (A), capreomycin (Cap), cycloserine (Cs), ethionamide (Et), protionamide (Pt), fluoroquinolones (Fq), paraaminosalicylic acid - PASK (PAS) and rifabutin (Rfb).

From the point of view of the effectiveness of chemotherapy, it is necessary to imagine that there can be four populations of tuberculosis mycobacteria in the focus of active specific inflammation, different in localization (extra- or intracellularly located), drug resistance and metabolic activity. Metabolic activity is great for extracellularly located mycobacteria in the wall of the cavity or caseous masses, less for extracellular ones in macrophages and very low for persistent bacteria[8].

With progressive and sharply progressive tuberculosis (infiltrative, miliary, disseminated fibrocavernous and caseous pneumonia), there is an intensive multiplication of mycobacteria in the patient’s body, their release into the tissues of the affected organ, spread through the hematogenous, lymphogenous and bronchogenic pathways, resulting in areas of inflammation, caseous necrosis develops. Most of the mycobacteria in this period are extracellular, and the part of the mycobacterial population that turned out to be phagocytosed by macrophages, due to the intense destruction of phagocytes, is again located extracellularly. Therefore, the intracellular localization of mycobacteria at this stage is a relatively short-term period in the life process of a multiplying mycobacterial population.

In terms of effective chemotherapy, the drug resistance of tuberculosis mycobacteria is of great clinical importance. In a large and actively breeding bacterial population, there is always a small number of wild mutants resistant to anti-TB drugs in the ratio of 1 mutant resistant to isoniazid or streptomycin per million, 1 to rifampicin per 100 million and 1 to ethambutol per 100 thousand sensitive tuberculosis mycobacteria.

When conducting proper and adequate chemotherapy, these mutants have no practical value. But as a result of improper treatment, when inadequate chemotherapy regimens and combinations of anti-TB drugs are prescribed, not optimal doses, the ratio between the number of resistant and non-resistant mycobacteria changes. Under these conditions, mainly drug-resistant microbes multiply — this part of the bacterial population increases.

In the context of ongoing chemotherapy, leading to a decrease in the mycobacterial population and suppression of the multiplication of mycobacterium tuberculosis, a part of mycobacteria, which are in a state of persistence, remain in the patient's body. Persistent mycobacteria are often detected only by microscopic examination, because when sowing on nutrient media they do not give growth. Such mycobacteria are called "sleeping" or "dormant", sometimes - "killed."

Isoniazid, rifampicin, ethionamide, ethambutol, cycloserine and fluoroquinolones have more or less the same activity against the intra- and extracellularly located mycobacterium tuberculosis. Aminoglycosides and capreomycin have significantly less bacteriostatic activity on intracellular mycobacteria. Pyrazinamide with a relatively small bacteriostatic activity enhances the action of isoniazid, rifampicin, ethambutol and other drugs, penetrates very well into the cells and has a pronounced activity in the acidic caseous environment.

The simultaneous administration of several anti-TB drugs (at least 4) allows to complete the course of treatment before the emergence of drug resistance of mycobacteria or to overcome their initial resistance to one or two drugs.

In connection with the different state of the mycobacterial population at different stages of the disease, the science-based is the division of tuberculosis chemotherapy into 2 periods or phases of treatment[9].

The initial (or intensive) phase of treatment is aimed at suppressing the rapidly multiplying and actively metabolizing mycobacterial population and the drug-resistant mutants contained in it, reducing its number and preventing the development of secondary resistance.

For the treatment of tuberculosis caused by drug-sensitive mycobacteria, 4 anti-TB drugs are used: isoniazid, rifampicin, pyrazinamide, ethambutol or streptomycin for 2 months and then 2 drugs - isoniazid and rifampicin for 4 months.

Isoniazid, rifampicin and pyrazinamide form the core of the combination when exposed to susceptible tuberculosis mycobacteria. It should be emphasized that isoniazid and rifampicin act equally effectively on all populations of mycobacteria located in the focus of tuberculous inflammation. At the same time, isoniazid has a bactericidal effect on all mycobacteria sensitive to both drugs and kills rifampicin-resistant pathogens. While rifampicin also kills mycobacteria sensitive to these two drugs, and, most importantly, bactericidal effects on isoniazid-resistant mycobacteria. Rifampicin effectively affects persistent mycobacteria if they begin to "wake up" and increase their metabolic activity. In these cases, rifampicin is more effective than isoniazid. The addition of pyrazinamide and ethambutol to the combination of isoniazid and rifampicin creates conditions for increasing their effect on the pathogen and prevents the formation of resistance of mycobacteria.

In cases of drug-resistant tuberculosis, the question arises of the use of reserve anti-TB drugs, the combinations of which and the duration of their administration have not yet been fully developed in controlled clinical trials and are still largely empirical.

The combination of fluoroquinolone, pyrazinamide and ethambutol is active against multidrug resistance strains but does not reach the level of activity of the combination of isoniazid, rifampicin and pyrazinamide against sensitive mycobacteria. This must be taken into account with the duration of the intensive phase of treatment for drug-resistant pulmonary tuberculosis.

The duration and effectiveness of the intensive phase of treatment should be based on indicators of the cessation of bacterial excretion by smear and culture of sputum, identified drug resistance and positive clinical and radiological dynamics of the disease.

The second phase of treatment is the effect on the remaining slowly multiplying and slowly metabolizing mycobacterial population, most of which are intracellular, in the form of persistent forms of mycobacteria. At this stage, the main task is to prevent the multiplication of the remaining mycobacteria, as well as the stimulation of reparative processes in the lungs using

various pathogenetic agents and treatment methods. Treatment must be carried out for a long period of time in order to neutralize mycobacteria, which, due to their low metabolic activity, are difficult to destroy with the help of anti-TB drugs.

The antibiotic treatment regimen for tuberculosis, that is, the choice of the optimal combination of anti-TB drugs, their doses, routes of administration (intravenously, intramuscularly, inhalation, etc.), the duration and rhythm of use (once or intermittently), is determined taking into account:

the epidemiological danger (contagiousness) of the patient when mycobacterium tuberculosis is detected in sputum by microscopy and culture on culture media;

the nature of the disease (first detected case, relapse, chronic course);

prevalence and severity of a specific process;

drug resistance of Mycobacterium tuberculosis.

Phase II and III clinical trials are currently underway for shortened treatment regimens with new drugs (e.g. fluoroquinolones) or new dosages of known drugs (e.g. rifamycin, rifapentin).

For the first time in nearly 50 years, two new molecular substances proposed for the treatment of multidrug-resistant TB (MDR-TB) undergo a regulatory process in the United Kingdom of Great Britain and Northern Ireland and the United States. Phase IIb and III of clinical trials of these two new drugs for the treatment of MDR-TB are currently underway.

In addition, studies are underway of other new components and new drug combinations for the treatment of CL-TB and / or MDR / XDR-TB.

In 2019 World Health Organization (WHO) some guidelines have been approved by the Guidelines Review Committee.

Below is one of the most recent guideline. This table is intended to guide the design of individualized, longer MDR-TB regimens.

Table.2.1.
Grouping of medicines recommended for use in longer MDR-TB regimens[10].

Groups & steps	Medicine
Group A: Include all three medicines	levofloxacin *OR* moxifloxacin
	bedaquiline

Groups & steps	Medicine
	linezolid
Group B: Add one or both medicines	clofazimine
	cycloserine *OR* terizidone
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	ethambutol
	delamanid
	pyrazinamide
	imipenem–cilastatin *OR* meropenem
	amikacin (*OR* streptomycin)
	ethionamide *OR* prothionamide
	p-aminosalicylic acid

2.2. New drug targets and antimycobacterial agents in discovery in tuberculosis

Recently, WHO proposed that all drugs directed against drug-resistant MBT strains be reclassified according to their potential efficacy. Rifampicin is not on the list of such drugs, but isoniazid in high doses (as mentioned earlier) is included. Fluoroquinolones (moxifloxacin, levofloxacin) are now classified as the first group of second-line anti-TB drugs because of their effectiveness, good penetration into body tissues, and because of satisfactory tolerance, although there are some side effects that need attention[11]. It should be noted that some fluoroquinolones are no longer recommended (ofloxacin, ciprofloxacin) due to their low effectiveness.

Fluoroquinolones are available and inexpensive. In some regions of the world, due to the widespread use of fluoroquinolones for the treatment of various infectious diseases that are not related to tuberculosis, the level of resistance of mycobacteria to them is high and may interfere with their use as anti-tuberculosis drugs[12].

Among the second-line injectable drugs, streptomycin is conditionally mentioned, namely, depending on the local level of resistance of mycobacteria, which can be high. Linezolid is now classified as one of the main drugs of the second row and has a pronounced bactericidal

effect, but is associated with frequent and severe hematological and neurological side effects[13]. Sutezolid, a drug of the same group, may have comparable efficacy with fewer side effects.

Clofazimine, originally developed as an anti-tuberculosis drug, but then used to treat leprosy, which was the main component of the "Bangladesh regimen" short course, can make a significant contribution to eliminating the persistence of mycobacterium tuberculosis. This drug is inexpensive, but it provokes frequent skin side effects[14].

Carbapenems (tebipenem ,imipenem, meropenem, ertapenem) are potent bactericides that also showed very good activity against tuberculosis[15]. Their effectiveness is increased due to the combination with clavulanates (amoxicillin / clavulanate). They are used by injection, but tebipenem is in the form of a tablet, which makes it easier to use.

One of the main problems associated with the appointment of second-line drugs is their high price, limited availability and frequent intolerance[16]. If second-line drugs are available, affordable and satisfactorily tolerated, some of them are highly effective. All modern guidelines recommend the use of one fluoroquinolone (cat A) in combination with one second-line injectable drug (cat B), two other main second-line drugs (cat C) and with the addition of drugs (cat D) depending on the drug sensitivity of the strains.

The recommendation to use at least five drugs shows its highly probable or documented effectiveness during the intensive phase when pyrazinamide is included in the treatment regimen (except if resistance to it is reliably known).

The recommended duration of treatment with this combination of drugs is 8 months. After this intense phase, an injectable drug is usually excluded from further treatment, which lasts for a total duration of an average of up to 20 months. The total duration of treatment depends on changes in bacteriological parameters, therefore, as a means of monitoring during the follow-up period and to evaluate the result of treatment, it is recommended that monthly culture studies be performed.

Several recently published studies have shown a high level of success in MDR-TB patients who received a short treatment regimen using 7 drugs during the intensive phase (4 to 6 months) and 5 drugs during the subsequent treatment phase. This so-called "Bangladesh regime" has attracted attention and is now included in the latest WHO guidelines because of its reduced duration and cost compared to the standard recommended regimen of 18 to 24 months, which is supported by WHO and most national guidelines[17].

It should be noted that this treatment regimen cannot be used in patients with resistance to several additional drugs, especially fluoroquinolones. In the case of resistance to fluorofinolones, the frequency of low efficacy of therapy in this scheme ranged from 87.4% to 51.0%[18]. Therefore, the latest WHO guidelines and some recent publications insist that the short-term

regimen can be applied only in specific conditions[19]. If the short-term regimen is used arbitrarily, without careful monitoring of drug resistance before treatment, it can create further resistance and stimulate the relapse or development of XDR-TB [27].

Almost 60 years after the release of the last active anti-TB drug (rifampicin), two new drugs have recently been released - Bedaquiline and Delamanid, which have been approved by some (but not all) regulatory authorities and will soon become available in most countries where there are MBU-TB both drugs seem to be very active against mycobacterium tuberculosis and have a satisfactory safety profile, although careful monitoring of the ECG is recommended when using them, because the QT interval can be extended, especially if these drugs are used in combination with others that exhibit similar side effects (moxifloxacin , clofazimine)[20].

According to recently issued WHO recommendations on the use of bedaquiline and delamanide, they should now be used only in patients with MDR / XDR MBT in whom an effective treatment regimen using five active drugs cannot be used due to the presence of additional resistance or intolerance existing drugs. Clinical trials will be ongoing, and it is possible that recommendations for the use of new drugs may change in the future. At the moment, there is no evidence that one drug is more preferable than another, although their mechanisms of action are very different[21].

A significant limitation of the use of bedaquiline and delamanide is the very high price of these drugs and their limited availability in many parts of the world. Both of these factors may change in the future with the adaptation of the market price, due to the introduction of generics and their wide distribution after approval by regulatory authorities[22]. However, one potential problem in the future is nevertheless expected - the emergence of resistance to one or both new drugs, which, unfortunately, has already been observed[23].

The simultaneous use of bedaquiline and delamanide is not recommended mainly because of insufficient evidence of their clinical efficacy and because of concern about the risk of prolonging the QT interval, although there are isolated cases of using both drugs without side effects and with a satisfactory outcome[24].

According to recent estimates, if the use of bedaquiline and delamanide was intended for patients at risk of adverse outcomes with modern available drugs, such as patients with resistance to fluoroquinolones, with XDR-TB, with a history of previous treatment with second-line drugs, with high bacillary load, with a low body mass index or past imprisonment, the use of one or both new drugs can be indicated in about two thirds of patients with MDR MBT[25]. However, the financial and logistical implications of such a decision can be significant[26].

Long before the advent of antibiotics, many attempts were made to improve the outcome of treatment in patients with tuberculosis. In general, all approaches used can be classified into the following categories:

1) Measures to restore immunodeficiency or increase the mechanisms of natural defense.

2) Measures to influence the infectious agent with the help of anti-TB drugs;

3) Measures that reduce the bacterial load[27].

Many measures have been proposed to improve defective defense mechanisms or to enhance the natural defensive ability of the immune system. The best known of these is the use of antiretroviral therapy in patients with HIV infection to restore the immune system's ability to control bacterial infection. The early initiation of antiretroviral therapy in patients with TB / HIV co-infection improves patient survival and reduces the spread of tuberculosis among high-risk groups[28].

Other measures, such as immunostimulation or additional administration of a variety of cytokines with IFN, are aimed at patients without initial immunodeficiency, but the results they demonstrate are contradictory and seem to be ineffective[29].

BCG vaccination has some effectiveness in protecting young children from severe and common forms of the disease in contact with tuberculosis, but its protective role in adults is much less convincing. Unfortunately, studies of new vaccines to date have not been successful[30].

Since the formation of granulomas can protect mycobacteria from the immune system and from the action of antibiotics, some studies have tried to destroy granulomas or prevent their formation using immunosuppressive drugs (anti-TNF and steroids) to demonstrate an accelerated bacteriological response or a reduced risk of relapse[31]. However none of these attempts did not reach general recognition and was fixed in practice[32].

Another approach is the administration of drugs by inhalation in order to achieve a high concentration near the granulomas. This method has been used experimentally to prescribe isoniazid, rifampicin, amikacin, pyrazinamide and levoflaccin and is promising, but drugs (except amikacin) are not available today for general use in the treatment of tuberculosis[33].

Measures to reduce the bacterial load were used long before the advent of antibiotics and were based on the assumption that the patient’s immune system can more easily cope with a limited number of bacteria than with a very large number of them. Collapsotherapy, in the form of thoracoplasty or therapeutic pneumothorax, and the surgical removal of infected lung tissue have been widely used, but with controversial results. Recently, attempts have been made to resume collapse therapy by positioning endobronchial valves in the airways of patients with intractable MDR / XDR-TB[34]. Recently published reviews of surgical interventions in cases where pharmacological treatment is ineffective. The recommendations were published by the

Regional Office for Europe of the World Health Organization (EURO / WHO) and the general opinion is that the role of surgery is significant in MDR / XDR-MBT tuberculosis, where pharmacological treatment is low and surgical treatment is necessary.

The mycobacterial fatty-acid biosynthesis pathway is responsible for the biosynthesis of fatty acids from acetyl-CoA, through the action of several synthases. This process is essential for bacterial growth, as fatty acids need to be synthesized by the cell. The biosynthesis is catalysed by a multi-enzyme protein named Fatty acid synthase (FAS). The class II of this enzymatic system can only be found in bacteria, turning the FAS-II system a possible selective antibacterial target.

Bedaquiline (Fig. 2) was approved in 2012 for use in treatment of MDR-TB by the Food and Drug Administration (FDA). It is marketed under the name Sirturo. Bedaquiline belongs to diarylquinolines class of compounds which is a recently emerged class of antitubercular drugs. In addition to this, including bedaquiline to current MDR-TB standard treatment regimen has proven to be cost-effective as well as cost-saving.

Unlike other drugs, bedaquiline targets the energy metabolism of mycobacteria. Though mycobacteria can survive under conditions of stress like hypoxia, nevertheless the production of energy molecule ATP by ATP synthase is essential for the survival of all sorts of mycobacteria whether active of dormant, replicating or nonreplicating, extracellular or intracellular, and fermenting or nonfermenting. The ability of bedaquiline to be bactericidal for both replicating as well as dormant bacteria could also shorten the prolonged TB treatment.

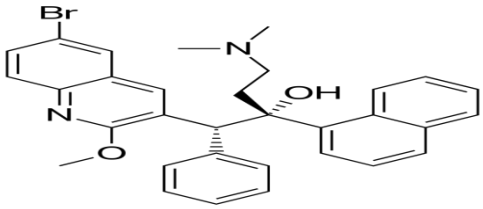

Fig.2. Bedaquiline

Delamanid (Fig. 3)is a drug of the nitroimidazole class approved by European Medicines agency for the treatment of MDR-TB infection. Amongst other clinically approved TB drugs, delamanid exhibits the lowest minimum inhibitory concentration and is found to be active against both drug-sensitive and drug-resistant M. tuberculosis strains. The drug also inhibits replicating and dormant as well as extracellular and intracellular isolates. However delamanid is not recommended for use in combination with bedaquiline by WHO as both are cardiotoxic. They cause QT prolongation, which is an alteration of the electrical activity of the heart .

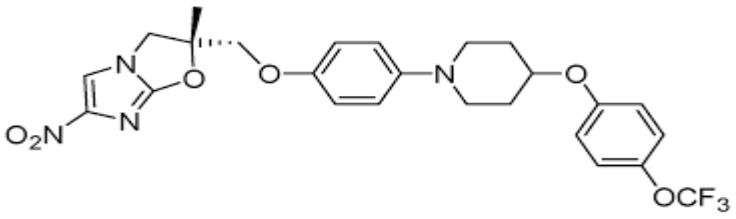

Fig. 3. Delamanid

Pretomanid like delamanid belongs to the nitroimidazole class of drugs. Like delamanid, pretomanid is also effective against both replicating and hypoxic nonreplicating strains of M. tuberculosis (Fig. 4).

Both these new TB drugs require activation since they are prodrugs and also exhibit a similar mechanism of action. Pretomanid undergoes bioreductive activation by Ddn enzyme, forming various metabolites by the reduction of the imidazole ring. One of the metabolites is a des-nitro derivative that releases nitric oxide which damages intracellular proteins, cell wall lipids, and various other macromolecules and turns out to be bactericidal for anaerobic bacteria. This des-nitro derivative is considered to be responsible for the antimycobacterial activity of pretomanid. However, studies suggest that aerobic bacteria are killed by pretomanid through the disruption of cell wall mycolic acid synthesis pathway, which in turn depletes ketomycolates and accumulates hydroxymycolates. Thus pretomanid shows a dual mode of action, inhibition of cell wall biosynthesis and respiratory poisoning. Although this mechanisms explain how pretomanid acts on replicating bacteria, it does not reveal the mechanism of action of pretomanid on latent cells.

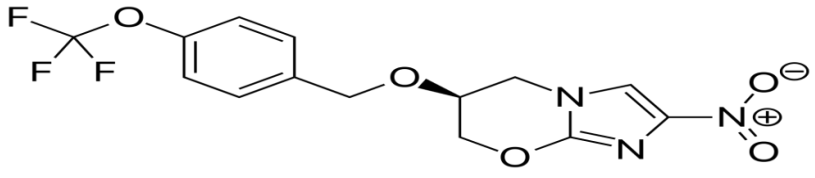

Fig. 4. Pretomanid

Linezolid (Fig. 5)belongs to oxazolidinone class and was initially approved for the treatment of infections caused by Gram-positive bacteria such as methicillin-resistant Staphylococcus and Vancomycin-resistant enterococcus, in the year 2000. It is sold under the brand name Zyvox. The first candidate of the oxazolidinone class was identified at E.I. du Pont de Nemours&Company in 1978. However, further development of this class of antibacterials was finished as clinical trials showed safety concerns specially hepatotoxicity. Later in 1990s, the development of resistance in Gram-positive bacteria led to reconsideration of the development of oxazolidinones, the FDA approved the first oxazolidinone drug linezolid for

clinical use in 2000. Later it was discovered that this drug is active not only against Gram-positive bacteria but also shows promising antimycobacterial activity .

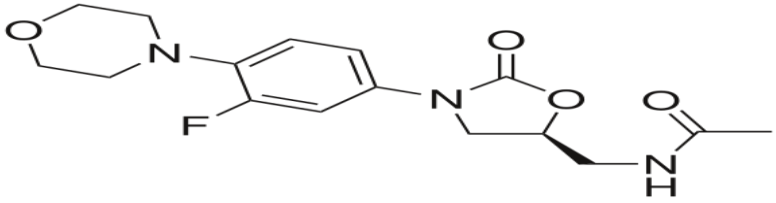

Fig. 5. Linezolid

Sutezolid(Fig. 6) was developed alongside linezolid in 1996. After lying undeveloped for several years sutezolid became the second most promising candidate of the oxazolidinone class after linezolid, active against M. tuberculosis. This drug was active against drug-resistant strains of M. tuberculosis and also showed favorable pharmacokinetics and low toxicity in rat models. After showing promising results in murine models it was studied on humans, and appeared to be safe and well tolerated .

Sutezolid is a thiomorpholine analogue of linezolid and its mechanism of action is similar to linezolid. It inhibits protein biosynthesis by binding to 235 rRNA of the large 50S subunit of ribosome. Sutezolid is converted to an active sulfoxide metabolite, which is more potent than sutezolid against extracellular TB. However, for the treatment of intracellular TB in pulmonary TB infection, the parent molecule, sutezolid was found to be 17 times more effective than its metabolite.

In addition, sutezolid is effective against both the drug-susceptible as well as the drug-resistant TB. The drug and its metabolite both show a relatively short plasma half-life (approximately 4 hours) which favors a divided dosage rather than a single dose. Sutezolid shows addictive effects with SQ109 and is also efficacious in combination with other new TB drugs.

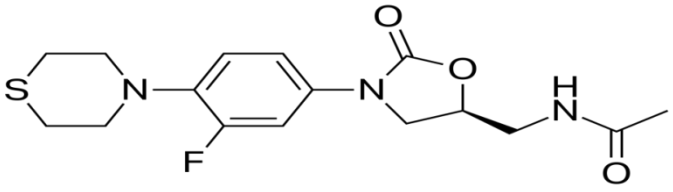

Fig. 6. Sutezolid

Fluoroquinolones are a class of very potent, broad-spectrum synthetic antimicrobial agents that are currently being explored for the treatment of TB. A survey on the antibiotic expenditure in the United States revealed that fluoroquinolones rank the highest, accounting for approximately one-fourth of the $10 billion antibiotic market.

Fluoroquinolones are fluorine derivatives of quinolones. Quinolones are bicyclic ring compounds, categorized into 2- and 4-quinolones. The most common clinically used quinolones

are the 4-quinolones All fluoroquinolones generally have a similar mechanism of action that targets DNA gyrase in Gram-negative bacteria and topoisomerase IV in Gram-positive bacteria.

Currently, fluoroquinolones like ciprofloxacin, ofloxacin and levofloxacin (Fig. 7) are recommended as second-line drugs for the treatment of TB whereas two candidates of the fluoroquinolone class, moxifloxacin (Fig. 8) and gatifloxacin are currently being evaluated for their promising anti-TB activity. Besides their efficacy, there are side-effects also associated with the use of both these compounds like gatifloxacin causes hyperglycemia / hypoglycemia whereas moxifloxacin shows cardiovascular risks.

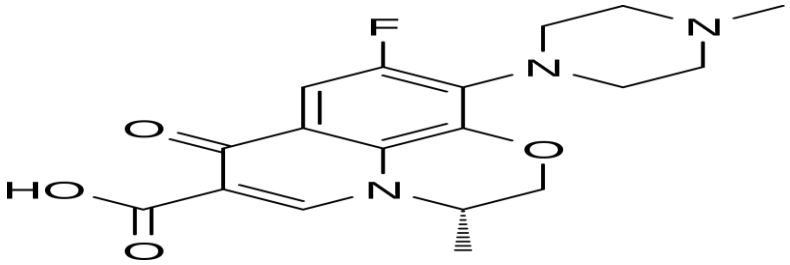

Fig.7. Levofloxacin

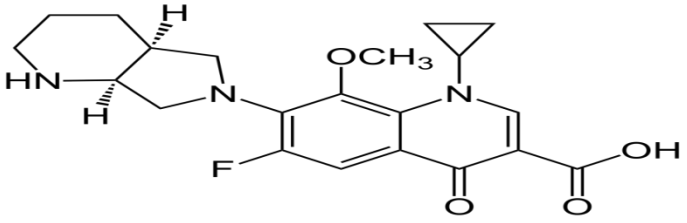

Fig. 8. Moxifloxacin

Clofazimine(Fig.9), a member of riminophenazine class of antibiotics. is an established antileprosy drug which is repurposed for the treatment of MDR-TB. The drug is sold under the brand name lamprene and was initially developed for the treatment of MDR-TB (Fig. 9).

Clofazimine exhibited significant antimycobacterial activity in vitro but further development of this drug was terminated as it was found to be therapeutically inefficient in humans showing side-effects like skin discoloration and mental disturbances. The simultaneous discovery of better agents for the treatment of TB resulted in loss of interest in antimycobacterial efficiency of clofazimine, Besides possesing antimicrobial properties, clofazimine also shows anti-inflammatory properties which can be of therapeutic use in nonmicrobial and inflammatory disorders of cutaneous origin.

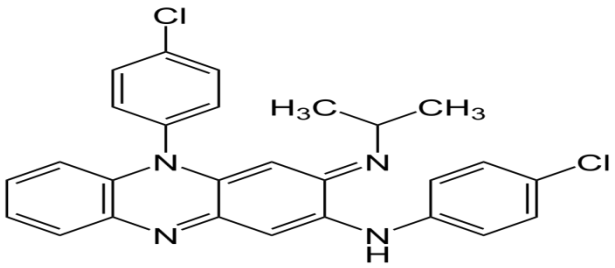

Fig. 9. Clofazimine

SQ109 (Fig. 10) is a 1,2-ethylenediamine currently in phase II clinical trial for DS-TB. This drug candidate targets MmpL3 protein of M. tuberculosis involved in cell wall synthesis. The structural design of SQ109 originated from ethambutol, an established first-line drug for the treatment of TB. SQ109 is active against ethambutol-resistant strains which indicate that the mode of action of SQ109 is different from ethambutol.

SQ109 is bactericidal against both MDR-TB and XDR-TB causing M. tuberculosis strains. In vitro studies SQ109 shows synergistic effects with isoniazid and rifampicin and additive effects with ethambutol and streptomycin.

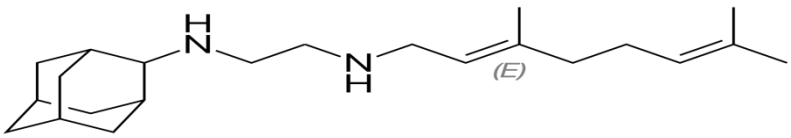

Fig.10. SQ109

PBTZ169 (Fig. 11)belongs to benzothiazinone (BTZ) class of drugs and is currently in phase II early bactericidal activity trials. PBTZ169 is a piperazinobenzothiazinone developed by optimizing the compound of benzothiazinone class .

PBTZ169 and BTZ043 show promising bactericidal activity against MDR-TB strains. Both the drug candidates are very potent against replicating bacilli but show low activity against nonreplicating bacilli.

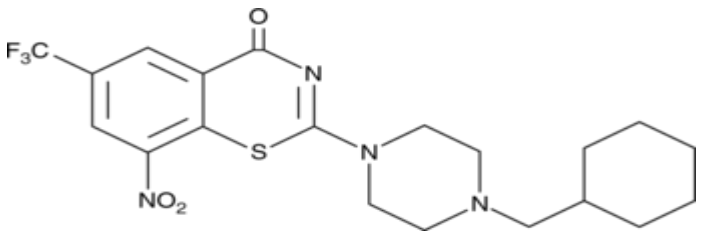

Fig. 11. PBTZ169

Q203 (Fig. 12) is an imidazopyridine amide identified through phenotype high-content throughput screening and is currently in phase II clinical trial. The compound was found to be active against MDR and XDR strains of M. tuberculosis. Q203 showed promising action against tuberculosis in mice. Besides Q203 has no chiral center which aids in the large-scale synthesis of

the compound. The reasonable cost of goods required for large-scale production of Q203 gives the compound another edge as tuberculosis largely affects low-income group countries[35].

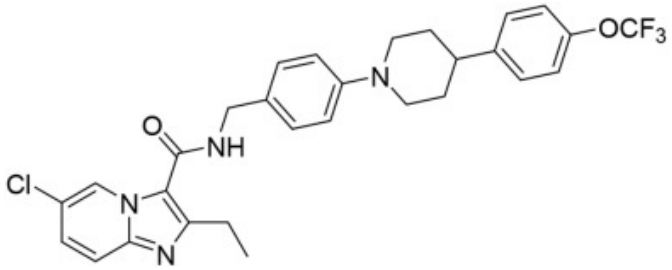

Fig. 12. Q203

Despite the structural differences between InhA, MmpL3, DprE1 and QcrB, many of the corresponding ligands identified by HTS are lipophilic compounds, which might reflect the fact that these targets are membrane proteins. This highlights the need for careful selection of hit compounds for hit-to-lead optimization, as highly lipophilic hit compounds may lead to toxicity that might be linked to inhibition of host membrane proteins or membrane integrity.

CONCLUSION

In general, the basic principles of TB treatment are as follows: treatment with several drugs in adequate doses for a sufficient time.

Unfortunately, these principles have been forgotten by doctors, TB control programs, and especially government financial agencies. As a result of this, errors are very common in the treatment of patients with MDRTB, and seeking expert advice is always justified.

Patients with AIDS and MDRTB are another confused group, as it is associated with the occurrence of other pulmonary infections requiring a long course of treatment, and the overall mortality rate is high.

Close collaboration with a reliable laboratory is crucial for the clinician in the treatment of MDRTB. Laboratory data should be analyzed in the general clinical aspect, they can never be ignored or blindly followed. There are various modes of anti-TB treatment for MDRTB, and the right choice depends on the results of a study of the sensitivity of MBT and data on previous drugs. If the clinical situation requires empirical treatment before obtaining the results of sensitivity, then from the main regimen should be added two to three drugs that the patient has not previously taken. In the future, after obtaining the results of sensitivity, the regimen can be adapted towards reducing the number of drugs.

Side effects of anti-TB drugs, especially second-line drugs in AIDS patients, require careful study and a large share of clinical decisions. On the one hand, the patient can be

persuaded to endure some gastrointestinal discomfort, itching or dizziness, at the same time, on the other hand, a temporary cessation of medication and / or correction of therapy can help to avoid deafness, blindness, liver or kidney failure. In addition, significant drug interactions are upsetting often, especially with RIF, and contribute to soreness and mortality in this patient population.

Surgical treatment can often help with MDRTB, when the main bacterial pool is localized and can be mostly removed by resection.

TB is a very complex disease with many different manifestations, and the diagnosis, treatment and dynamic monitoring of HIV patients, children, as well as patients with extrapulmonary TB, requires extensive knowledge, experience and clinical thinking.

Most anti-TB drugs act on bacteriostatic mycobacterium tuberculosis, inhibiting their reproduction and reducing their virulence. Isoniazid and rifampicin can act bactericidal in high concentrations.

To obtain a lasting therapeutic effect and prevent possible relapses, anti-TB drugs should be used for a long time. The choice of drugs and the duration of their use depend on the form of tuberculosis and its course, previous treatment, the sensitivity of tuberculosis mycobacteria to the drug, its tolerance, etc. When combining drugs, 1 or 2 drugs of the first row should be kept in combination, especially isoniazid, if there are no contraindications or drug resistance to it. With combined use, the dose of each of the drugs taken is usually not reduced.

It is very important to remember that the degree of resistance to some major drugs, for example, isoniazid, is variable and depends on what specific genetic mutation is present[36]. For example, with a mutation involving the inhA site, mycobacteria may be partially sensitive to isoniazid, and this drug can be used, especially if it is prescribed in doses higher than usual. This confirms the need for drug susceptibility tests both with suspected drug resistance and with proven drug resistance, and gene typing of the strain with the definition of the exact mutation can be of great importance for choosing the appropriate drug treatment[37].

Several drugs currently used to treat drug-resistant tuberculosis have been developed to fight other diseases, such as leprosy or severe life-threatening bacterial infections. Among the drugs that were originally developed for purposes other than the treatment of tuberculosis, but which exhibit activity against tuberculosis mycobacteria, the most practically important are fluoroquinolones, clofazimine, carbapenems and linezolid.

The last decade experienced a surge in the development of new drugs, repurposed drugs, and various treatment regimens.

The drugs with poor in vitro efficacy, like ethambutol and pyrazinamide, efficient in vivo

due to their excellent biodistribution. Drugs like bedaquiline and delamanid contain two or more aromatic moieties, which make them highly lipophilic (tLegP values of 7.3 and 5.6. respectively). High lipophilicity makes the formulation difficult and leads to unnecessary drug-drug interactions, though high lipophilicity decreases drug distribution in specific microenvironments. Thus, it is anticipated that careful designing of new molecules will lead to the development of new compounds that could solve all the problems which society is facing.

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